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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,969	07/24/2001	Yukio Kawamura	3479-4000US1	4744

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EXAMINER

HELMS, LARRY RONALD

ART UNIT PAPER NUMBER

1642

DATE MAILED: 10/30/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/911,969

Applicant(s)

KAWAMURA ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 August 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 1 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☒ Certified copies of the priority documents have been received in Application No. 09/023,731.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3. 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of Group II, claims 2-12 in Paper No. 7 is acknowledged.
2. Claim 1 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 7.
3. Claims 2-12 are under examination.

### ***Specification***

4. The disclosure is objected to because of the following informalities:

The use of the trademark SOLR has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

### ***Claim Objections***

5. Claims 2-12 are objected to because of the following informalities:

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a. Claims 2-12 depend on non elected claim 1. Claims 2-12 will be examined with the limitations recited in claim 1.

b. Claim 1 contains a misspelled word "whcih" and the subject and verb do not agree (sequence which have).

Appropriate correction is required.

***Oath/Declaration***

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: There is a non-initialed change for the residence of Tomohide Saka. The term "Noble" has been altered.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 4 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 4 is indefinite for reciting "derived from *Tricholoma matutake*" because the exact meaning of the phrase is not clear. It is not clear how the nucleic acid is "derived". Is the nucleic acid sequence changed or altered or is the nucleic acid from *Tricholoma matsutake*?

b. Claim 10 contains the trademark/trade name SOLR, SURE, TOPP. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe SOLR, SURE, TOPP and, accordingly, the identification/description is indefinite.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-2, 4-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleic acid encoding the protein of Pestka (U.S. Patent 6,300,474) and a nucleic acid which encodes a protein comprising SEQ ID

NO:1 and a nucleic acid of SEQ ID NO:2 and vectors and host cells comprising such nucleic acids and a method of preparing the protein encoded by said nucleic acids, does not reasonably provide enablement for a nucleic acid which encodes a modified amino acid sequence of SEQ ID NO:1 which have antitumor activity wherein one or more amino acids are added and/or inserted into SEQ ID NO:1 and/or one or more amino acids are substituted and/or deleted in SEQ ID NO:1 and pharmaceutical compositions comprising which is used as antitumor agent . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims broadly encompass a nucleic acid which encodes a modified amino acid sequence consisting of SEQ ID NO:1 which have additions, insertions, substitutions, and deletions and which retain activity as well as in vitro and in vivo pharmaceutical compositions for use as antitumor agents. The claims also broadly read on a nucleic acid which encodes for a protein in which every residue of SEQ ID NO:1 has been deleted or substituted.

The specification teaches a nucleic acid of SEQ ID NO:2 which encodes a protein consisting of SEQ ID NO:1 (556 amino acid residues)(see page 3, lines 12-14). The specification teaches that when the protein consisting of SEQ ID NO:1 was given to cells which had been transformed by SV40 and human papiloma virus the quantity of tested protein necessary for 50% fatal activity of total cells was 10 ng/ml in SVT2, 100 ng/ml in A3 cells, and 15-20 ng/ml in HPV16 cells (see page 9, lines 25-34). The specification fails to enable the myriad of nucleic acids which encode proteins encompassed by the claims which contain numerous deletions, insertions, substitutions, etc. as well as enablement for the protein for in vitro or in vivo antitumor activity.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138, IDS #3). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252, IDS #3).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987, IDS #3). Removal of the amino terminal histidine of glucagon substantially decreases

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the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975, IDS #3).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation of the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results.

In view of the unpredictability in protein chemistry as evidenced by Burgess et al, Lazar et al, Schwartz et al , and Lin et al, and the lack of guidance, lack of examples, and lack of predictability associated with regard to producing the myriad of proteins and using the myriad of nucleic acids encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

11. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.



Claim 9 is rejected under 112 first paragraph because it is unclear if the cell lines COP-5 and C127 are known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed COP-5 and C127 cell lines, a suitable deposit for patent purposes, evidence of public availability of the claimed cells or evidence of the reproducibility without undue experimentation of the claimed cells, is required.

***Claim Rejections - 35 USC § 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

13. Claims 2, 4, 5, 6, 7, 8, 9, and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Pestka (U.S. Patent 6,300,474, filed 6/9/95).

The claims recite a nucleic acid that encodes a modified amino acid sequence with deletions and/or insertions and/or substitutions which the protein has antitumor

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activity, which is derived from *Tricholoma matutake* and pBluescript SK(-) vector comprising the nucleic acid, *E. coli* host cell comprising a vector, and a method of producing the polypeptide. For this rejection all the limitations of claim 1 will be read into claims that depend on claim 1 and because of the indefinite nature of the term "derived" in claim 4 this claim is included in the rejection and is interpreted to mean the nucleotide can be altered from that from *tricholoma matsutake*.

Pestka teach the nucleic acid which encodes a protein that is an antitumor protein and vectors, host *E. coli* cells and methods of producing such proteins (see columns 2, 4, line 48, 10, claims 2, 4, 9). Because claim 1 recites the protein has one or more deletions, insertions, or substitutions, the art of Pestka reads on the claims.

### ***Claim Rejections - 35 USC § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 2, 4-10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pestka (U.S. Patent 6,300,474, filed 6/95) as applied to claims 2, 4-9, and 12 above, and further in view of Nagata et al (U.S. Patent 5,874,546, Filed 3/94).

Claims 2, 4-9, and 12 and the interpretation has been described supra. Claim 10 recites wherein the E. coli cell is JM109.

Pestka has been described supra. Pestka also teach a wide variety of expression vectors and host systems exist for expression (see column 2, lines 30-36). Pestka does not teach JM109. This deficiency is made up for in the teachings of Nagata.

Nagata et al teach nucleic acids, vectors, and host cells, especially JM109 cells (see column 10, lines 40-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the JM109 cell of Nagata et al with the nucleic acid of Pestka.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the JM109 cell of Nagata et al with the nucleic acid of Pestka because Pestka teach there are a wide variety of systems and host cells for expression (see column 2) and Nagata et al teach the JM109 transformants can be easily sorted depending on their resistance against drugs and enzymatic activity (see column 10).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### ***Conclusion***

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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18. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

A handwritten signature in black ink, appearing to be 'L. Helms', written in a cursive style.